Psychiatric hospitalization following antipsychotic medication cessation in first episode psychosis

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Abstract

Background

There are questions about the risk-benefit balance of longer-term antipsychotic medication treatment following first episode psychosis, especially in relation to relapse because of dopamine supersensitivity following treatment cessation.

Aim

To determine whether hospitalization rates in first episode psychosis patients are associated with length of initial oral antipsychotic medication exposure.

Methods

We examined psychiatric hospitalization rates in patients experiencing first episode of psychosis from the total population of Sweden between 1 January 2007 and 31 December 2016 (N=7043). We categorized patients by the length of first antipsychotic treatment (<6m, 6m to <1yr, 1yr to <2yrs, 2yrs to <5yrs and ≥5yrs).

Results

Compared to those treated for <6 months, individuals receiving oral antipsychotic medications for ≥5 years had less than half the cumulative incidence of hospitalization at all times between 1 and 4 years after treatment cessation.

Conclusion

We found no evidence that hospitalization rates increased with increasing baseline antipsychotic exposure.

Declaration of interest

None.

Introduction

Guidelines recommend continuing antipsychotic treatment following first episode of psychosis (FEP) for 1-2 years (Correll et al., 2018). In recent years, questions have been raised about the necessity of longer-term treatment in this population (Leucht, 2018). It has been argued that prolonged antipsychotic treatment may increase rebound psychosis and relapse risk, potentially via dopamine supersensitivity (Murray et al., 2016). We are aware of only one population-based study which supports this hypothesis (Tiihonen et al., 2018) and there is limited, discrepant evidence from studies in animals and humans (Goff et al., 2017). We aimed to determine hospitalization rates in individuals with FEP following different lengths of first antipsychotic treatment (<6m, 6m to <1yr, 1yr to <2yrs, 2yrs to <5yrs and ≥5yrs).

Methods

For this study we used Swedish linked National Patients registers, which have complete population coverage from 1973 and 2006 for inpatient and outpatient services respectively, and the Prescribed Drug register, which is complete from 1 July 2005 onwards. We limited our definition of FEP to individuals receiving a diagnoses of schizophrenia (ICD-9: 295A-E, G, W, X; ICD-10: F20) and non-affective psychoses (ICD-9: 297, 298B-E, W, X; ICD-10: F21-24, F28-F29) in the National Patient Register after 1 January 2007. As we wanted to study an incident FEP cohort we only included individuals aged 16-35 and excluded individuals who received a diagnosis of schizophrenia, non-affective psychosis or bipolar disorder, or were treated with antipsychotic medication, before 1 January 2007. We categorized first oral antipsychotic medication exposure as: <6m, 6m to <1yr, 1yr to <2yrs, 2yrs to <5yrs and ≥5yrs. We used prescription dates and a three-month repeat prescription window to define periods of continuous prescribing in patients with ≥2 prescriptions. Individuals were followed up from the date they stopped taking antipsychotic medication to

the earliest of: psychiatric hospitalization, restarting antipsychotic medication, death, migration out of Sweden, or 31 December 2016. We performed Fine-Gray competing risks regression (Fine and Gray, 1999; Austin and Fine, 2017) with psychiatric hospitalization as the outcome and restarting antipsychotic medication or death as competing events. This produces a subdistribution hazard ratio, which is the difference in rate between exposure groups in patients who are event free or have experienced a competing event (reintroduction of antipsychotic medication, or death), and estimates the cumulative incidence function for hospitalization.

We adjusted for age, sex, calendar year, diagnosis (schizophrenia vs. non-affective psychosis), percentage of days spent as inpatient during first antipsychotic exposure (as a proxy for severity), history of substance misuse diagnosis, and antipsychotic type at baseline (using the seven antipsychotic medication neuroscience based nomenclature groupings Zohar et al., 2015). Ethical approval for the study was obtained via the Regional Ethical Review Board in Stockholm.

Results

Psychiatric hospitalization occurred in 1,323 of the 7,043 patients during follow-up (Figure 1, Table 1). There was an inverse relationship between duration of the patient's first oral antipsychotic exposure and cumulative incidence of hospitalization (Figure 2). Individuals exposed to antipsychotic medication for ≥5 years had an adjusted subdistribution hazard ratio of 0.44 (95% confidence interval 0.26-0.75) compared to those exposed for <6 months (Table 2).

Discussion

Duration of baseline antipsychotic treatment was inversely associated with rate of hospitalization after stopping treatment in FEP. Compared to those treated for <6 months,

individuals receiving antipsychotic medications for ≥5 years had less than half the cumulative incidence of hospitalization at all times between 1 and 4 years after treatment cessation. In all groups, hospitalization rate was most rapid in the first 6 months after treatment cessation.

Our results run contrary to the findings of Tiihonen and colleagues (2018), the only previous study of this type in a population cohort of which we are aware. Tiihonen et al., (2018) found lowest hospitalization rates in patient's never stopping antipsychotics, then those stopping immediately, with increasing rates over increasing duration of treatment before cessation. An analytical difference is that they used a Cox proportional hazards model, whereas we considered the competing risk of restarting antipsychotic medication, which substantially modifies the chance of hospitalization (Fine and Gray, 1999). However, if we treat our data in the same way (censoring at the point of restarting antipsychotic medication), we find no association between baseline antipsychotic exposure length and hospitalization, so this does not explain the discrepancy. Our cohort contained no one permanently exposed to antipsychotics and no one stopping immediately; such individuals may be atypical FEP cases. Our competing risks approach gives a more accurate estimate of cumulative incidence of hospitalization.

Despite multivariable adjustment, our results remain vulnerable to unmeasured confounding, especially relating to confounding by indication, and time-modified confounding. Our approach may misclassify antipsychotic exposure periods, and we cannot guarantee that repeat collection of prescriptions means adherence to medication, but this would bias our results toward the null.

Our study does not support the hypothesis that longer antipsychotic medication exposure increases the rate of relapse after stopping treatment. Although this hypothesis has been widely discussed in recent years (Leucht, 2018; Murray et al., 2016; Tiihonen et al., 2018),

there is not yet consistent compelling clinical or preclinical evidence to endorse it (Goff et al., 2017).

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Figure 1. Flow diagram of potentially included patients

Figure 2. Hospitalization incidence in the first 4 years following antipsychotic cessation by length of baseline exposure, from fully adjusted competing-risks regression model

Table 1. Patient characteristics by duration of antipsychotic treatment

	Duration of antipsychotic treatment in first episode psychosis				
Baseline characteristics	**<6m**	**6m to <1yr**	**1yr to <2yrs**	**2yrs to <5yrs**	**≥5yrs***
N	3,045	1,838	1,196	821	143
Age, median (IQR)	24.73 (21.19-29.14)	24.91 (21.02-29.69)	25.37 (21.19-29.82)	24.58 (20.70-29.12)	25.67 (22.25-29.68)
Female, N (%)	1,011 (33.20)	620 (33.73)	443 (37.04)	308 (37.52)	47 (32.87)
Schizophrenia diagnosis, N (%)	638 (20.95)	478 (26.01)	356 (29.77)	318 (38.73)	76 (53.15)
Percentage of days spent as inpatient during first treatment, range	0-86%	0-82%	0-40%	0-48%	0-46%
Substance misuse, N (%)	1,241 (40.76)	685 (37.27)	433 (36.20)	266 (32.40)	46 (32.17)
Second generation antipsychotic, N (%)	2,689 (88.31)	1,609 (87.54)	1,065 (89.05)	746 (90.86)	130 (90.91)

* Mean 6.34, standard deviation 1.04 years

Table 2. Psychiatric hospitalization after antipsychotic cessation

	Duration of antipsychotic treatment in first episode psychosis				
	<6m	**6m to <1yr**	**1yr to <2yrs**	**2yrs to <5yrs**	**≥5yrs[1]**
N (%)	653 (21.44)	341 (18.55)	196 (16.39)	117 (14.25)	16 (11.19)
Follow-up time, Person-years (1000s)	5.05	2.54	1.39	0.74	0.08
Adjusted SHR (95% CI)*	1 [baseline]	0.84 (0.73-0.98)	0.73 (0.60-0.88)	0.55 (0.43-0.69)	0.44 (0.26-0.75)

* Adjusted subdistribution hazard ratio and 95% confidence interval. Adjusted for age, sex, calendar year, diagnosis (schizophrenia vs. other non-affective psychosis), percentage of days spent as inpatient during first antipsychotic exposure, history of substance misuse diagnosis, and antipsychotic type (using neuroscience based nomenclature groupings). The subdistribution hazard ratio should be interpreted as the difference in rate between exposure groups in patients who are event free (e.g., not been hospitalized) or have experienced a competing event (restarting antipsychotic medication or death).